REMARKS

Reconsideration of the application is respectfully requested in view of the above amendments and following remarks. Claims 1-23 were pending in the present application. Claims 18-22 were withdrawn by the Examiner due to a restriction requirement. Claims 1-17 and 23 are rejected. Claims 1, 7, 8, 14, 15 and 16 have been amended. Claims 6, 13 and 17 have been canceled. Claims 1-5, 7-12, 14-16 and 23 are currently pending in the present application.

Claims 6, 13 and 17 have been cancelled without prejudice to filing a divisional application directed to the subject matter claimed therein.

Claim 1 has been amended by a) replacing "alky" with "alkyl" to correct at typographical error; b) by defining A as benzodioxane and dihydrobenzodioxane as required by the restriction requirement and without prejudice to pursuing the deleted definitions of A in a divisional application; and c) by adding the definitions for the terms "aryl", "cycloalkyl", "cycloheteroalkyl" and "heteroaryl". Support for adding the definitions of aryl, cycloalkyl, cycloheteroalkyl and heteroaryl can be found on page 29, line 28 to page 30, line 28 of the specification. Support for adding the definition of A is dihydrobenzodioxane is found in Examples 1, 36-49, 58-61 and 64-67 of the specification.

Claims 7 and 14 have been amended by defining A as benzodioxane and dihydrobenzodioxane as required by the restriction requirement, and without prejudice to pursuing the deleted definitions of A in a divisional application. Support for adding the definition of A is dihydrobenzodioxane is found in Examples 1, 36-49, 58-61 and 64-67 of the specification.

Claim 8 has been amended by a) by defining A as benzodioxane and dihydrobenzodioxane as required by the restriction requirement, and without prejudice to pursuing the deleted definitions of A in a divisional application; and b) by adding definitions for the terms "aryl", "cycloalkyl", "cycloheteroalkyl" and "heteroaryl". Support for adding the definitions of aryl, cycloalkyl, cycloheteroalkyl and heteroaryl can be found on page 29, line 28 to page 30, line 28 of the specification. Support for adding the definition of A is dihydrobenzodioxane is found in Examples 1, 36-49, 58-61 and 64-67 of the specification.

Claims 15 and 16 have been amended by deleting the compounds that are not benzodioxane derivatives to comply with the restriction requirement, without prejudice to pursuing the deleted compounds in a divisional application.

No new matter has been added to the above-captioned application by the above amendments.

REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH
FOR LACK OF ENABLEMENT

The Examiner stated that Claims 1-17 and 23 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for benzodioxane compounds where R1, R2, R4, R6 and Ra-h are pyridyl, does not reasonably provide enablement for the broader scope in claim 1 and the claims dependent thereon. The Examiner also stated that the scope of 4-7 membered heterocyclic rings having 0-2 additional heteroatoms is not adequately enabled and that the specification shows only pyridyl described in actual working examples.

Applicants respectfully disagree. Applicants submit that rejected Claims 1-17 and 23 of the present application are described in the specification in a way sufficient to enable one skilled in the art to make and use the entire scope of the claimed invention.

The present application provides examples of compounds in which R1 and R2 are phenyl rings. Specifically, Examples 1, 36-46. 58-59 and 64-67 of the specification provide benzodioxane derivatives (dihydrobenzodioxane compounds) in which R1 and R2 are phenyl rings. The specification also provides guidance as to which rings would be suitable in the definitions of R1, R2, R4, R6 and Ra-h in the claims and on pages 29-30 of the specification where the terms aryl, cycloalkyl, cycloheteroaryl and heteroaryl are defined. One of skill in the art, a chemist, would understand the scope of the claims based on these definitions.

Applicants further assert that section 112 does not require working examples (*In re Strahilevitz*, 668, F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982)) and that the applicants claim scope is not necessarily limited only to those embodiments actually disclosed in the specification (See *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); see also *Utter v. Hiraga*, 845 F.2d 998, 6 U.S.P.Q.2d at 1714 ("A specification may, within the meaning of 3 USC 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses"), and that the embodiment need not necessarily have even been reduced to practice (See In re Wright, 999 F.2d 1557; 1561, 27 U.S.P.Q.2d 1510, 1513).

The Examiner indicated that the limited data provides no clear evaluation of how the remaining scope might affect potency and that there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are structurally so dissimilar as to be chemically non-equivalent.

Applicants submit that the compounds of the present invention are cannabinoid-1 receptor antagonists/inverse agonists and as such are useful to treat diseases mediated by the antagonism or inverse agonism of the cannabinoid-1 receptor, including the diseases disclosed in the specification, such as obesity. Using the assays provided on pages 162 and 163 of the specification, one of ordinary skill in the art can readily determine if a compound works as a cannabinoid-1 receptor antagonist or inverse agonist and is useful to treat diseases and disorders related to the antagonism or inverse agonism of the cannabinoid-1 receptor.

The Examiner also stated that the specification only provides some examples of what the terms may signify, but does not limit cycloheteroalkyl, heteroaryl and heterocyclic ring to any particular definition.

Applicants disagree. The terms aryl, cycloheteroalkyl, heteroaryl and heterocyclic ring are adequately defined in the specification of the present application. The term "aryl" is specifically defined on page 29, line 33 to page 30, line 3 of the specification as "mono- or bicyclic aromatic rings containing only carbon atoms, including aryl group fused to a monocyclic cycloalkyl or monocyclic cycloheteroalkyl group in which the point of attachment is on the aromatic portion". The term "cycloalkyl" is specifically defined on page 29, lines 28-32 of the specification as "mono- or bicyclic or bridged saturated carbocyclic rings, each having from 3 to 10 carbon atoms, including monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion". The term "cycloheteroalkyl" is specifically defined on page 30, lines 14-18 of the specification as "a mono- or bicyclic or bridged saturated rings containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen, including a monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion". The term "heteroaryl" is specifically defined on page 30, lines 4-6 of the specification as "a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms". Given this definition one of skill in the art, a chemist, can readily determine if a compound falls within the definitions of aryl, cycloalkyl, cycloheteroalkyl and heteroaryl, and within the scope of the claims.

However to expedite prosecution, Applicants have amended Claims 1 and 8 to:

a) define aryl as "phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrohbenzo-furanyl, dihydrobenzopyranyl, and 1,4-benzodioxanyl". Support for this amendment is found in the listed examples of cycloheteroalkyls on page 30, lines 1-3 of the specification.

b) define cycloalkyl as "cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, and indanyl". Support for this amendment is found on page 29, lines 31-32 of the specification.

c) define cycloheteroalkyl as "pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, pyranyl, tetrahydrofuranyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolinyl, morpholinyl, dioxanyl, oxanyl, tetrahydroisoquinolinyl, dihydroindolyl, dihydroisoindolyl, perhydroazepinyl, 2-pyridine, 4-pyridone, N-substituted-(1H, 3H)-pyrimidine-2,4-diones, and N-substituted uracils". Support for this amendment is found in the listed examples of cycloheteroalkyls on page 30, lines 18-28 of the specification.

d) define heteroaryl as "pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzotriazolyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and oxazolidinyl". Support for this amendment is found in the listed examples of heteroaryls on page 30, lines 4-13 of the specification.

Claims 2, 3, 4, 5, 7 and 23 depend from Claim 1 and incorporate the amendments to Claim 1. Claims 9, 10, 11, 12, 14, 15 and 16 depend from Claim 8 and incorporate the amendments to Claim 8.

Applicants have canceled Claims 6, 13 and 17 without prejudice to filing a divisional application directed to the subject matter claimed therein. In view of the cancellation of Claims 6, 13 and 17, the rejection of Claims 6, 13 and 17 under 35 USC 112, first paragraph is moot and should be withdrawn.

In view of the above arguments, the cancellation of Claims 6, 13 and 17, and the amendments to Claims 1 and 8, Applicants respectfully submit that the present Claims are adequately enabled and request reconsideration and withdrawal of the rejection of Claims 1 – 17 and 23 under 35 USC 112, first paragraph.

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REJECTION UNDER 35 U.S.C. 112. SECOND PARAGRAPH FOR INDEFINITENESS

The Examiner stated that Claims 1-17 and 23 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention.

Applicants submit that rejected Claims 1-17 and 23 of the present application are described in the specification in a way as to point out and distinctly claim the subject matter that the applicants regard as the invention, and that the invention is described in the specification in a way that is sufficient to enable one skilled in the art to make and use the entire scope of the claimed invention.

The Examiner stated that: 1) numerous substituent variables make it impossible to determine the full scope of the claimed subject matter, and that the subject matter cannot be regarded as being a clear and concise description, and as such the claims are indefinite; and 2) Claim 17 does not reasonably provide enablement for treating a disease mediated by the Cannabinoid-1 receptor.

As discussed in the 112 first paragraph rejection above, Applicants have amended Claims 1 and 8 to incorporate the definitions of "aryl", "cycloalkyl", "cycloheteroalkyl" and "heteroaryl", and have canceled Claims 6, 13 and 17. Claims 2, 3, 4, 5, 7 and 23 depend from Claim 1 and incorporate the amendments to Claim 1. Claims 9, 10, 11, 12, 14, 15 and 16 depend from Claim 8 and incorporate the amendments to Claim 8. Additionally, Claims 15 and 16 are directed to specific compounds found in the Examples 1-67 on pages 147 – 162 of the specification and are therefore definite.

The Examiner also indicated that the specification does not enable any physician skilled in the art of medicine to make the invention commensurate in scope with these claims due to the quantity of experimentation necessary.

Applicants disagree. The specification discloses both how to make and use the claimed invention. The synthetic methods in the text, schemes and examples on pages 61-162 of the specification show how to make the compounds of the present invention.

The specification also discloses how to use the compounds of the present invention. As stated in *In re Bundy*, 209 U.S.P.Q. 48, 51 (CCPA 1981), the how to use requirement of 112 is satisfied by "disclosure of some activity coupled with the knowledge as to the use of this activity." The specification of the instant application provides such a disclosure. The specification discloses a method for

determining the cannabinoid -1 receptor binding affinity and the cannabinoid-1 receptor functional activity on pages 162-163 (See Examples 68 and 69).

The specification also gives guidance and examples sufficient for treating disorders mediated by the cannabinoid-1 receptor, including obesity. The specification provides a statement of the utility of the claimed compounds, which are cannabinoid antagonists/inverse agonists, on page 33, line 24 to page 34, line 2. The utility of cannabinoid-1 receptor antagonist/inverse agonists to treat obesity, asthma and cirrhosis of the liver in addition to other diseases is further disclosed in the literature references listed in the specification on pages 1-3. As noted in the specification, the at least one CB-1 modulator characterized as an inverse agonist or antagonist, SR141716A (also known as Rimonabant or Acomplia(R)), was in clinical trials for the treatment of eating disorders, and has since been approved in Europe for the treatment of obese patients. Based on these disclosures in the specification, Applicants submit that the how to use requirement of 112 is satisfied.

Applicants further submit that the specification provides guidance that sufficient for treating disorders, including obesity, and that would allow the skilled artisan to practice the instant invention without undue experimentation. The court has held that "[A] considerable amount of experimentation is permissible, if it is merely routine, or is the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (*In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404 (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). One of ordinary skill in the art can readily identify the compounds of formula I useful in the methods of the present invention. As disclosed above, using the assays provided on pages 162 and 163 of the specification, one of ordinary skill in the art can readily determine if a compound works as a cannabinoid-1 receptor antagonist or inverse agonist and is useful to treat diseases and disorders related to the antagonism or inverse agonism of the cannabinoid-1 receptor. Applicants submit that a reasonable amount of guidance with respect to experimentation is given in the specification.

The Examiner indicated that since none of the claimed compounds have been used to treat any human disease, and that a skilled physician would not know what dose to use for each of these different diseases. The Examiner also indicated that there is no working example of treatment of any disease in man or animals.

Applicants disagree. The specification teaches how to use the claimed compounds including a detailed description of routes of administration and dosages. Specifically, the dosage ranges of 0.001 mg/kg to 100 mg/kg of body weight are listed on page 35, line 26 to page 36, line 30; and the routes of administration for the compounds of the present invention are recited as "oral, rectal, topical, parenteral, ocular, pulmonary, nasal" on page 35, lines 9-26. Applicants submit that the specification sufficiently

describes how the compounds of the present invention can be used and sufficiently describes how and in what dosage the compounds of the present invention can be administered.

As previously noted, the utility of cannabinoid-1 receptor inverse agonists/antagonists, including the compounds of the present invention, is disclosed in the specification and in the art. Additionally, Applicants submit that in vitro and in vivo testing of each embodiment of the invention is not required under section 112, first paragraph. Section 112 does not require working examples (*In re Strahilevitz*, 668, F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982)) and that the applicants claim scope is not necessarily limited only to those embodiments actually disclosed in the specification (See *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); see also *Utter v. Hiraga*, 845 F.2d 998, 6 U.S.P.Q.2d at 1714 ("A specification may, within the meaning of 3 USC 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses"), and that the embodiment need not necessarily have even been reduced to practice (See In re Wright, 999 F.2d 1557; 1561, 27 U.S.P.Q.2d 1510, 1513).

Applicants further submit that although the claimed invention has not yet been tested in human clinical trials for safety and effectiveness to determine suitable doses, such trials are not required to establish utility under the patent law:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating the incentive to pursue, through research and development, potential cures in many crucial areas... *In re Brana*, 34 U.S. P.Q.2d 1436, 1442-3 (Fed Cir. 1995)

In summary, the instant specification provides a teaching of how to use the invention which would be credible to the person of ordinary skill in the art and which would permit the skilled artisan to use the claimed compounds for the stated utility without undue experimentation.

Given the specification disclosures of: 1) the utility of cannabinoid-1 receptor inverse agonists/antagonists to treat obesity and other cannabinoid-1 receptor modulated disorders; 2) the screening assays for cannabinoid-1 receptor inverse agonists/antagonists; 3) the routes of administration of the claimed compounds; 4) the dosage ranges for treating obesity, and other cannabinoid-1 receptor

modulated disorders; and 5) the literature support for the utility of cannabinoid-1 receptor inverse agonists/antagonists to treat obesity, and disorders mediated by the antagonism or inverse agonism of the cannabinoid-1 receptor, Applicants respectfully submit that Claims 1-17 and 23 are enabled and definite, and should be allowed.

Applicants have canceled Claims 6, 13 and 17 without prejudice to filing a divisional application directed to the subject matter claimed therein. In view of the cancellation of Claims 6, 13 and 17, the rejection of Claims 6, 13 and 17 under 35 USC 112, first paragraph is moot and should be withdrawn.

In view of the above arguments, cancellation of Claims 6, 13 and 17, and amendments to Claims 1 and 8, Applicants respectfully submit that the present Claims are adequately enabled and definite, and request reconsideration and withdrawal of the rejection of Claims 1-17 and 23 under 35 USC 112, first paragraph.

Applicants believe that all of the rejections have been overcome and therefore earnestly solicit an early Notice of Allowance.

Respectfully submitted,

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